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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/792,374	03/03/2004	Ronald Levy	9692-000042	5030

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EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/792,374	LEVY ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-136* is/are pending in the application.

4a) Of the above claim(s) *91-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *80-90* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments and Amendment

The Amendment filed on 11/29/06 in response to the previous Non-Final Office Action (9/25/06) is acknowledged and has been entered.

In the amendment, claims 1-79 have been cancelled. Claim 80-136 have been added and are currently pending. Newly added claims 113-123 are drawn to a method comprising providing a plurality of primer, employing real time PCR and providing a database and claims 91-102, 103-112, or 124- 136 are drawn to a method for determining a probability of survival of a patient having DLBCL comprising measuring plurality of gene (91-102), amplifying a plurality of primer (103-112), amplifying plurality of genes (124-136). Applicants have originally elected invention (group I), drawn to a method for classify a patient having DLBCL comprising measung, normalizeing , correlating expression of pluraltiy of gene in a patient, while curently newly added claims 91-136) reciting related method, but having different steps and objectives, which are distinct from originally elected invention. It is noted that these claims belong to group III in the restsriction requirment dated 7/14/2005. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 91-123 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Thus, claims 80-136 are pending, claims 91-136 are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to a non-elected inventions. Claims 80-90 are under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

The following office action contains NEW GROUNDS of rejection.

Rejections Withdrawn

All the rejections comprising the rejection under 35 U.S.C. 112 second paragraph, the rejection under 35 U.S.C. 112, first paragraph, the rejections under 35 U.S.C. 102(b) and rejections under 35 U.S.C. 103 are withdrawn in view of the cancellation of all the claims.

The following is a New Ground of rejection-based on newly addition of claims

Claim Objection

Claim 80 is objected to for typographical error as "BLC2" in the formula, line 13. Amending the claim to "BCL2" would obviate this objective. Appropriate correction is required.

Under 35 U.S.C. 112, second paragraph

Claims 88 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recites "consists essentially of" rather than "comprising". It is unclear which elements or genes are excluded from the listed genes or sequences in the claims or which steps are intended to be omitted from the method claims by the new claim language. There is no clear definition provided in the specification for ingredients are steps that would materially affect the method. Therefore, the "consisting essentially of" language in the claim is being interpreted as "comprising". See the MPEP § 2111.03.

Under 35 U.S.C. 112, first paragraph

Drawn to new matter

Claims 88 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that the newly added claims 88 recites "consisting essentially of" in the claims. There is no written support for excluding any elements from the claimed method in the disclosure. Applicant has also not pointed to any disclosure that teaches which elements would alter the basic and novel characteristics of the invention. Therefore, it remains unclear what is to be materially excluded that would alter the invention. There is no teaching in the specification that would differentiate what is considered to

be materially altering to the skilled artisan. The Office is not requiring a list of specific materials that would have to be excluded from the claimed method, but a general teaching of properties that would effect the invention. It is applicant's burden to teach what would materially alter the characteristics of the claimed invention. See *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964) and *Ex Parte Hoffman*, 12 USPQ2d 1061, 1063-64. With this type of teaching, the skilled artisan would be able to readily discern what would be excluded from the "consisting essentially of" claim language. However, since there is no general teaching of this kind in the specification, the claim is rejected because it introduces new matter into the disclosure.

Drawn to enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims are drawn to a method for classifying a patient having diffuse large B-cell lymphoma (DLBCL) by measuring, normalizing, correlating the gene expression comprising LMO2, BCL6, FN1, CCN2, SCYA3, BCL2 and classifying a patient into a classification based upon weighed predictor Z in formula below:

Z= (AxLMO2)+(BxBCL6)+(CxFN1)+(DxCCN2)+(ExSCYA3)+(FxBCL2)

wherein the A-F are defined as -0.03, -0.2, -0.2, .03, 0.2, or 0.6 respectively in the claims and further drawn to Z value, <-0.06 indicates high probability of survival and from -0.06 to 0.09 indicates medium probability of survival and >0.09 indicates low probability of survival.

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The method objective of claims is classifying a patient and predicting the probability of survival of DLBCL patient based on gene expression levels calculated by the formula above. Thus, it would be expected that one of skill in the art would be able to do so without undue experimentation by using the claimed method comprising the formula.

The specification on page 22, table 3, teach levels of gene expression comprising the six genes listed in the formula normalized to housing keeping gene GAPDG in Raji cells. The specification on figure 1 teaches that predictive power (univariate score) with negative score associated with longer overall survival and positive associated with shorter overall survival based on the gene ranking comprising the six genes. On this figure, the formula is listed. The specification on figure 2B shows a Kaplan-Meier curves of survival (low, medium, high) defined by a prediction model based on the weighted expression of six genes (LMO2, BCL6, FN1, CCN2, SCYA3, BCL2). The specification on page 25, further teaches the Z calculated with the formula as survival prediction model and indicate that negative LMO2 means longer survival and positive weight on CCND2 mean shorter survival. However, The specification neither provides a method of how to use the formula based on the normalized expression levels of the six gene for calculating the Z value, nor a nexus between the factors (A-F) in the formula and expression levels of

the six genes indicated in the table 3. The specification provides no teaching on the relationship of Kaplan-Meier survival curve and Z value in the formula. Basically, the specification does not how to use and how to establish the formula. The examples in the specification provide no teaching on using Z value calculated by the formula for classifying the DLBCL patient and predicting the overall survival rate of DLBCL patient. Thus, the formula disclosed in the specification does not likely to be practiced or usedfor classifying DLBCL patients. Therefore, one of skill in the art would not use the claimed method based on the teaching provided in the specification. Rosenwald et al., (N Engl J Med, vol 346, page 1937-47, June, 2002, provided in previous office action) disclose a method of calculating overall survival of DLBCL patient by Cox proportional-harzards model based on combined the four gene-expression signatures and BMP6 gene (page 1944, col 1, and page 1945, fig 4-B). Rosenwald et al., teach neither claimed six genes nor the Z value calculated from formula for classifying or predicting the survival rate for DLBCL patients. Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000) although, disclose a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes comprising LMO2, BCL-6, and BCL-2 from the samples of DLBCL patients, no formula or only six genes are used for the classification.

Since the specification does not provide sufficient guidance or evidence how to use the formula for classifying and predicting the survival rate of DLBCL patients, which allows one of skill in the art to practice claimed method with a reasonable expectation of success, one of skill in the art would be forced into undue experimentation before practicing the claimed invention. If Applicants has any objective evidence or support contrary to the rejection, Applicant is invited to submit it to the Office for reconsideration.

Conclusion

No claim is allowed.

The formula in claim 80 is free of prior art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000) disclose a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes comprising LMO2, BCL-6, and BCL-2 from the samples of DLBCL patients normalized to the control expression comprising Raji cell (page 508-509 and fig 4, and page 510, column 2, para 2). Alizadeh et al., also disclose that method predicts the correlation of patient survival with gene expression in the classification groups comprises overall survival after treatment with anthracycline-based chemotherapy (page 509, column 2, fig 5 and page 510, line 15-19). Alizadeh et al., do not teach or suggest the formula in claim 80 and do not classify the patient and predict survival probability of the DLBCL patient based on the Z value calculated by the formula.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

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